Abstract submitted for the NAS Symposium on Toxicity Pathway-Based Risk Assessment 2009 Washington, DC May 11-13th

Application of the ToxMiner Database: Network Analysis Linking the ToxCast Chemicals to Known Disease-Gene Associations

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The US EPA ToxCast™ program is using *in vitro* HTS (High-Throughput Screening) methods to profile and model bioactivity of environmental chemicals. The main goals of the ToxCast program are to generate predictive signatures of toxicity, and ultimately provide rapid and cost-effective alternatives to animal testing. The chemicals selected for Phase I are composed largely by a diverse set of pesticide active ingredients, which had sufficient supporting *in vivo* data included as part of their registration process with the EPA. Other miscellaneous chemicals of environmental concern were also included. Application of HTS to environmental toxicants is a novel approach to predictive toxicology and health risk assessment, and differs from what is required for drug efficacy screening in that biochemical interaction of environmental chemicals are sometimes weaker than that seen with drugs and their intended targets. Additionally, the chemical space covered by environmental chemicals is much broader compared to that of pharmaceuticals.

The ToxMiner database has been created and added to the EPA's ACToR (Aggregated Computational Toxicology Resource) chemical database. One purpose of the ToxMiner database is to link biological, metabolic, and cellular pathway data to genes and *in vitro* assay data for the initial subset of chemicals screened in the ToxCast Phase I HTS assays. Also included in ToxMiner is human disease information, which correlates with ToxCast assays that target specific genetic loci. We have implemented initial pathway inference and network analyses, which allow linkage of the types of adverse health outcomes with exposure to chemicals screened in Phase I. This approach allows for the exploration of disease at a higher level of cellular and organismal organization, focusing on multiple, related disorders, and will possibly aid in the understanding of common disease outcomes (*e.g.* cancer or immune disorders) that are characterized by locus heterogeneity. Through the use of the ToxMiner database and the analysis framework presented here, we hope to address relationships between potential disease states in humans and environmental chemicals, as well as contribute to the larger goals of toxicogenomics by clarifying the role of gene-environment interactions in disease states. *Although this work was reviewed by EPA and approved for publication, it may not necessarily reflect official Agency policy.*